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| 09/980,484 | 03/25/2002 | Jacques Alexandre Hatzfeld | USB 99 AH CNR SOMA | 5595 |

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/980,484 | HATZFELD ET AL. | |
| | Examiner | Art Unit | |
| | Thaian N. Ton | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-17 are currently pending. Applicants' Amendment, filed 10/25/04, has been entered. Claims 1-17 have been amended. Claims 1-16 are under current examination.

### *Election/Restrictions*

Applicant's election with traverse of Group I (Claims 1-16) in the reply filed on October 25, 2004 is acknowledged. The traversal is on the ground(s) that the determination of lack of unity is improper and request that the lack of unity determination be withdrawn. Applicants argue that the Official action does not comply with the requirements of PCT Rules 13.1 and 13.2 because there is no citation of reference showing the common core exhibited by the compounds of present claims 1 and 2 (see p. 10 of Applicants' Response). Applicants further argue that the claims in groups I and II share a special technical feature, which is that both methods utilize non-differentiated cells of the present invention. See p. 2 of Applicants' Response.

This is not found persuasive because the identified special technical feature, as identified by Applicants is found to be methods of utilizing non-differentiated (*i.e.*, undifferentiated) cells. Undifferentiated cells are known in the art as evidenced by Xi *et al.* [**Br. Journ. Of Haematology**, 93:265-272 (1996)], who teach using umbilical cord blood containing non-differentiated $CD34^+$ cells, thus it is

found that the claims lack unity and the restriction requirement is found to be proper.

Finally, with regard to the species election requirement, upon further consideration, the Examiner withdraws this requirement. Thus, the claims will be examined with regard only to Group I (claims 1-16). Claim 17 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/25/04.

The requirement is still deemed proper and is therefore made FINAL.

### *Information Disclosure Statement*

Applicants' IDS, filed 12/3/01, has been considered.

### *Claim Objections*

Claim 15 is objected to because of the following informalities: the claim recites "comprises comprising" in lines 2-3 of the claim. The claim further recites "at the original of skin" in part (a) of the claim. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are directed to methods of maintaining a non-differentiated state of stem cells, while allowing cell division by administering an effective amount of an inhibitor of cell development in a controlled manner to maintain the non-differentiated state of the stem cells, while allowing their cell division. In further embodiments, the stem cells are human cells, selected from the group consisting of embryonic stem cells at the origin of somatic stem cells, stem cells/somatic progenitors at the origin of blood and/or various solid tissues. See claims 1 and 2, for example. While the method steps are simply set forth in the claims, the disclosure lacks adequate written description for the materials required to practice the claimed invention. Specifically, the embodiments of "embryonic stem cells at the origin of somatic cells," stem cells at the origin of "various solid tissues," and the specific "inhibitor of cell development," because these cells are not adequately described by the instant specification.

*Vas-Cath Inc. v. Mahurkar* 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification fails to provide appropriate description for the claimed embodiments of "embryonic stem cells at the origin of somatic stem cells, " stem cells at the origin of blood, and various other tissues", with any particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification, and which are not conventional in the art, as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient, relevant identifying characteristics (as it relates to the invention as a whole), such that one of skill in the art would recognize that Applicants had possession of the claimed invention. In the instant case, the claimed embodiments of *embryonic stem cells at the origin of somatic cells*, and *stem cells at the origin of blood, and various other tissues*, lack a written description. The specification fails to provide any description of embryonic

stem cells at the origin of somatic cells, because embryonic stem cells are pluripotent cells isolated from an embryo, and are thus, not considered somatic cells. Furthermore, claimed embodiments, such as stem cells at the origin of blood and various other tissues, fails to have a description, because the skilled artisan could not envision such stem cells, as encompassed by the claims, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention, and a reference to a potential method of isolating it. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP § 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

*Nature of the invention:* The claims are directed to methods for maintaining a non-differentiated state of stem cells, while allowing cell division of said stem cells, comprising administering to said stem cells an effective amount of an inhibitor of cell development in a controlled manner to maintain the non-differentiated state of stem cells, while allowing their cell division. In further embodiments, the stem cells are human cells, selected from embryonic stem cells at the origin of somatic stem cells, and/or stem cells/somatic progenitors at the origin of blood and/or various solid tissue; the inhibitor is selected from products of genes which control

cell development with respect to cell differentiation and/or cell division, inhibitors of cycline-dependent kinases, factors which control apoptosis or aging, and cytokines. In further embodiments, the claims are directed to processes for the multiplication of stem cells in a culture medium comprising stimulating stem cells in the resting state so that they are brought out of their resting state by neutralization of an inhibitor of cell development, produced by the cells and/or present in the culture medium so that there is an initiation of a number of cell divisions ranging from 1 to about 100, and inhibiting the stem cells in their differentiation with the aid of an inhibitor of cell development. The invention is complex in that it involves the maintenance of stem cells in an undifferentiated state while allowing them to divide.

*Breadth of the claims*: The claims are extremely broad in that they encompass utilizing any inhibitor of cell development in order to maintain any stem cell in an undifferentiated state, while allowing cell division.

*Guidance of the specification and/or existence of working example.* The specification is directed to the culture of human stem cells, and in particular, $CD34^+$ cells which contain hematopoietic stem cells. The specification teaches that an inhibitor of cell development encompasses any substance, which inhibits cell proliferation and/or cell growth and/or cell differentiation. See p. 2, lines 14-15. Particularly, that these inhibitors can include products of genes which control cell development with respect to cell differentiation and/or cell division, inhibitors of

cycline-dependent kinases, factors which control apoptosis or aging and cytokines (such as interferons or TGF-beta). See p. 3, lines 10-15.

The specification further teaches that the term "stem cells" encompasses immature cells, cells which are not differentiated (or non-differentiated), primitive cells, or pluripotent or multipotent cells. See p. 2, lines 30-32. These stem cells can encompass embryonic stem cells at the origin of somatic cells, stem cells/somatic progenitors at the origin of blood and/or various solid tissues (for example, skin, liver, etc.). See p. 2-3, bridging ¶. The specification teaches a prophetic working example with regard to the multiplication of hematopoietic stem cells (HSCs). Particularly, that the HSCs are obtained from umbilical cord blood and characterized by the marker, $CD34^+$. These $CD34^+$ cells are tested by the HPP-Q test (high proliferative potential-quiescent cell) such that the HSCs are cultured in the medium containing at least one inhibitor of cell development, such as TGF-β for 14-28 days, and these cells are then compared to cells that have not been cultured with an inhibitor of cell development to observe the proliferative potential of the cells (see pp. 12-13). The specification teaches that $CD34^+$ cells were incubated with an medium without serum comprising cytokines and an inhibitor of TGF-β (anti-TGF-β) and screening was subsequently carried out to evaluate the $CD34^+$ and $CD38^-$ test by HPP-Q. See pp. 13-14.

*State of the art.* At the time of Applicants' invention (filing date of 6/3/99), the state of the art of culturing stem cells with any particular inhibitor to maintain

them as undifferentiated but allow them to divide, is found to be unpredictable. For example, the leukemia inhibitor factor (LIF), which is found to keep mouse ES cells in an undifferentiated state, fails to prevent the differentiation of primate ES cells. See, for example, Thomson [**PNAS**, 92:7844-7848 (August 1995)], *Abstract*, and p.7844, 1st column, 1st ¶ who state that, "Mouse ES cells remain undifferentiated through serial passages when cultured in the presence of LIF and differentiate in the absence of LIF." Further, they state that, "R278.5 (*i.e.*, primate ES cells) cells remain undifferentiated when grown on mouse embryonic fibroblast layers but differentiate or die in the absence of fibroblasts, despite the presence of recombinant human leukemia inhibitory factor." See *Abstract*, emphasis added. Thus, the breadth of the claims fails to be predictably supported by the state of the art, which teaches that a specific factor which may work for one stem cell, may not work for another.

This is further underscored by specific teachings of Xi *et al.* [**Br. Journ. Of Haematology**, 93:265-272 (1996)], who compare the mechanisms of platelet factor 4 (PF4) and TGF-β1 on the growth of megakaryocyte (MK) progenitor cells in $CD34^+$ cells. Xi teach that although both PF4 and TGF-β1 inhibit MK development from $CD34^+$ cells, they show different effects in this inhibition. Where the inhibition of PF4 is found to be reversible, the inhibition using TGF-β1 is not. See *Abstract* and p. 270, *Discussion*. The breadth of the claims with regard to the use of any inhibitor to produce the required effect is not predictably supported by the specification.

Furthermore, Xi teach that TGF-β1 belongs to a superfamily which consists of five isoforms, where it is found that TGF-β1 is considered the most potent inhibitor of megakaryocytopoiesis. The amount of TGF-β1 needed to induce inhibition is far less than the amount of PF4 needed. See p. 265-266, bridging ¶.

*Predictability of the art.* The state of the art clearly shows that the particular stem cell and factor used to inhibit differentiation of that stem cell is unpredictable. There is no specific guidance provided by the instant specification with regard to a specific amount of a specific factor to be used with a specific type of stem cell in order to produce the claimed result. Thus, as evidenced by the state of the art, cited previously, the art of culturing stem cells in an undifferentiated state is found to be unpredictable. Furthermore, given the lack of teachings or working examples provided by the specification, it is found that it would have been unpredictable for the skilled artisan to practice the claimed invention.

*The amount of experimentation necessary.* In order to practice the claimed invention, the skilled artisan would have to first isolate a particular stem cell, determine a particular factor that results in the inhibition of differentiation, but allows for cell division and further, determine the amount of factor needed to provide sufficient inhibition of differentiation. The claims recite steps of administering "an effective amount" of an inhibitor to the stem cells. However, the specification provides no guidance or teachings with regard to how much an "effective amount" encompasses. As evidenced by the state of the art, as well as the

predictability in the art, it would have required undue experimentation for one of skill in the art, to determine how much is considered an "effective amount" with regard to the breadth of the claims.

Thus, when taken with the lack of any particular and specific guidance provided by the specification for the specific factors, specific stem cells and specific conditions to culture the stem cells in, to achieve inhibition of differentiation, yet allow for cell division; the lack of working examples, the breadth of the claims, with regard to any particular stem cells and any particular factor, it would have required undue and unpredictable experimentation for one of skill in the art to practice the claimed invention.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "high initial cell concentration" in part (a), line 9 of claim 15 is indefinite because it is a relative term. The term "high initial cell concentration" is not defined by the claim, and the specification does not provide a standard for

ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 15, part (e) is unclear because it recites "which corresponds to a total duration of ..." It is unclear what "which" refers to – the amplification factor, or the repetition of cycles of division and resting. Appropriate correction is required.

*Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-7, 8-10, 12, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams *et al.* [**Nature**, 336:684-687 (15 December 1988)].

The claims are directed to methods for maintaining a non-differentiated state of stem cells while allowing cell division, comprising administering an effective amount of an inhibitor of cell development in a controlled manner to maintain the non-differentiated state of stem cells, while allowing their cell division. In further embodiments, the inhibitor is selected from the group consisting of genes which

control cell development with respect to cell differentiation and/or cell division, inhibitors of cycline-dependent kinases, factors which control apoptosis or aging, cytokines. In further embodiments the claims are directed to a process for multiplication of stem cells in a culture medium comprising stimulating stem cells in the resting state, so that they are brought out of their resting state by neutralization of an inhibitor of cell development, produced by the cells or is present in the culture medium so that there is an initiation of a number of cell divisions ranging from 1 to about 100, and inhibiting said stem cells in their differentiation with the aid of an inhibitor of cell development. In further embodiments, the multiplication process maintains the cells in a non-differentiated state, the cells are present in a concentration of about 1 to about $10^{10}$ cells per ml; the inhibitor of cell development is synthesized by the stem cells and/or is added to the culture medium containing the stem cells; wherein the inhibitor of cell development is chosen from the group consisting of genes which control cell development with respect to cell differentiation and/or cell division, inhibitors of cycline-dependent kinases, factors which control apoptosis or aging, cytokines.

Williams teach the culturing of mouse ES cells in the presence of leukemia inhibitory factor (LIF), which is a molecule that induces differentiation in myeloid leukemic cells. See *Abstract.* They teach that in order to test whether LIF could maintain the stem-cell phenotype of ES cells, four independently derived ES cell lines were cultured in concentrations of 1,000-5,000 units per $ml^{-1}$ and it was found

that more than 95% of the colonies displayed the stem cell phenotype of compact colonies. See pp. 684-5, bridging ¶. Williams further teaches that long-term maintenance of the four ES cell lines in LIF for up to 22 passages (approximately 100 cell generations) did not alter the growth characteristics of the cells and they maintained the stem-cell phenotypes. See p. 685, 2nd ¶.

Accordingly, Williams anticipates the claimed invention.

Claims 1-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Xi *et al.* [**Br. Journ. Of Haematology**, 93:265-272 (1996)].

Xi compare the mechanisms of platelet factor 4 (PF4) and TGF-β1 on the growth of megakaryocyte (MK) progenitor cells in $CD34^+$ cells. Xi teach that although both PF4 and TGF-β1 inhibit MK development from $CD34^+$ cells, they show different effects in this inhibition. Where the inhibition of PF4 is found to be reversible, the inhibition using TGF-β1 is not. See *Abstract* and p. 270, *Discussion.* Xi teach using $10^5$/ml of $CD34^+$ cells and incubating the cells with either 5 mg/ml of PF4 and 1 ng/ml of TGF-β1. See p. 266, 2nd column, Liquid culture system. The cells were then incubated for 2 days. See p. 267, 1st column, 1st sentence. The effects of this culturing were then analyzed by direct immunofluorescent assays and by flow cytometry. See p. 267, 1st column.

Accordingly, Xi anticipate the claimed invention.

Claims 1, 2, 4, 5-9, 12, 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Moore *et al.* [U.S. Pat. No. 6,084,060, filed March 28, 1997].

Moore teach methods of regulating hematopoietic processes by providing a factor and method of using the factor to maintain and expand hematopoietic progenitor cell populations. See col. 2, lines 47-52. They teach a protein, pylartin, which can be used in culturing hematopoietic stem cells of various species which allows the preservation of the progenitor cells yet, is able to inhibit the differentiation of the cells. See col. 6, lines 22-47. They teach that the pylartin protein can be used in conjunction with flk2 ligand in an amount sufficient to selectively expand the progenitor cells, without inducing differentiation. See coll. 8, lines 18-22. They teach the isolation of the pylartin protein from kidney beans and hyacinth beans. See Example 1. They teach the that the pylartin protein preserves both human and murine hematopoietic progenitor cells *in vitro* when cultured with the cells. See Example 2. They teach that when used in conjunction with IL1 and FL, human hematopoietic progenitors were preserved for 2 weeks, and that the number of colonies derived from the functional progenitors is several times greater than compared to controls. In particular, they teach that cord blood mononuclear cells were cultured at a concentration of 800,000 cells in 4 ml. See Example 8.

Accordingly, Moore anticipate the claimed invention.

*Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzfeld *et al.* [**Exp. Hematology**, 25(8):777 (1997), Meeting Abstract Number 174)].

Hatzfeld teach that TGF-β down-modulates various cytokine receptors, and that this effect can be suppressed within 6 hours by the addition of anti-TGF-b antibodies, or antisense nucleotides. Hatzfeld study the release from TGF-β growth

inhibition of high proliferative potential-quiescent primitive progenitors to understand whether this inhibitor is a central regulator of the stem cell compartment. They teach that these observations are used in developing an *in vitro* assay which combines receptor induction by anti-TGF-β together with optimal cytokine stimulation which can be performed using non purified hematopoietic progenitors. They teach that this method can render quiescent primitive progenitors responsive to optimal combinations of cytokines to improve the *in vitro* expansion of clinical samples. Thus, they teach the neutralization of an inhibitor of cell development (i.e., TGF-β).

Although Hatzfeld do not specifically teach that the cell divisions range from 1 to 100 (as required by claims 4, 5), it would be obvious for one of ordinary skill in that by allowing the cells to divide, there would be at least one cell division that occurs. Furthermore, although they do not specifically teach a cell concentration of about 1 to about $10^{10}$ cells (see claim 8, for example), it would be obvious for one of ordinary skill in the art that in order to implement the claimed invention there would have to at least be one cell present. Accordingly, the claimed invention would be rendered obvious by the teachings of Hatzfeld.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

*Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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